DIGITALIS AND DIURETICS IN HEART FAILURE WITH REGULAR RHYTHM, WITH ESPECIAL REFERENCE TO THE IMPORTANCE OF ETIOLOGIC CLASSIFICATION OF HEART DISEASE

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There is probably complete agreement today that digitalis affects the signs and symptoms of congestive heart failure most satisfactorily in the presence of auricular fibrillation. There is widespread agreement among American clinicians and investigators that a certain number of patients with heart failure and normal sinus rhythm respond to the administration of digitalis almost as satisfactorily as do those with auricular fibrillation, and many believe that such patients belong chiefly to the group designated as "chronic myocarditis" or "myocardial insufficiency." While this view has been expressed by many excellent observers, it remained for Luten (1) to bring forward the most convincing evidence in its support by a careful study which was the first to provide adequate control observations.

That there are several factors which influence the response of the regular heart to digitalis has long been recognized. More than a decade ago, Cohn (2) pointed out that rhythm alone was not a sufficient basis for the division of patients if the effect of digitalis was to be studied, and emphasized that the presence or absence of hypertension and the presence or absence of edema had to be considered. The value of a division into the groups which he suggested has been amply demonstrated by later work. Christian (3), Windle (4), Eggleston (5) and others have called attention to the importance of the *stage* of heart failure, stating that even when favorable results from digitalis are obtained at one time, the response to treatment becomes less satisfactory with each succeeding episode of failure.

These three conditions—abnormal blood pressure, edema, and the stage of heart failure which has been reached at the time treatment is begun—have been emphasized as exerting an influence upon the effect of digitalis on the regular heart. Comparatively little has been said of the importance of the etiology of heart disease in this connection, probably because it is only recently that heart disease has been classified on the basis of etiologic types. Most of those who have studied syphilitic heart disease agree that treatment is highly unsatisfactory after symptoms of failure make their appearance. Scott's (6) careful study of twenty-five patients in whom the diagnosis was proved by post mortem examination is particularly convincing: of his twenty-four individuals with heart failure, twenty "ran a progressive downhill course to death." Four were benefited by treatment, but the improvement was temporary; all were readmitted to the hospital after a brief period and died in less than a year.

Observations upon similar groups of patients with rheumatic heart disease are not available, probably because the normal rhythm seldom persists in such patients to the stage of advanced heart failure. Eggleston (5) remarks that heart failure due to rheumatic disease usually responds to treatment better than that associated with arteriosclerosis or syphilis, but he is referring to the earlier stages of congestive failure. In his recent book, Coombs (7) speaks thus of the later stages:

> "This brings me to the last kind of cardiac failure seen in cardiac rheumatism—progressive ventricular failure. . . . . In its fully developed form it is not often seen in cardiac rheumatism—nothing like so often as in the final phases of the hyperpietic or the senile heart. When it does appear, one may suspect that aortic incompetence, pericardial adhesion, or active myocarditis is at the bottom of it. Partly because these are all refractory to treatment, partly because failure of the ventricular cells is so fundamental a kind of failure, treatment achieves little success here."

It is the purpose of this paper to call attention to the importance of etiologic classification of heart disease in estimating the results of digitalis therapy, and to add certain observations concerning the action of digitalis and diuretic drugs upon the signs and symptoms of heart failure in the presence of a regular rhythm. It should be emphasized at the outset that many observations which have been interpreted as

indicating excellent results from the administration of digitalis to patients with the normal cardiac rhythm are entirely unacceptable because the observers failed to take into account the influence of bodily rest. This criticism has been made by more than one student of the subject, and requires only to be mentioned to be recognized as valid. A very brief experience in the treatment of heart failure serves to convince one that in any study of the effect of digitalis a preliminary period of rest without medication is not merely important: it is absolutely essential. It is clear, however, that this preliminary rest period is essential to the proper interpretation of results only when benefit follows the administration of the drug.

METHOD OF STUDY

The method of study, at least with regard to digitalis, was quite similar to that followed by Luten (1), although a number of the patients here reported were studied before the appearance of his paper. Briefly, it consisted of selecting adults with advanced congestive heart failure and considerable edema, with regular cardiac rhythm and without evidence of nephritis, and placing them at complete rest with no medication other than necessary sedatives. The fluid intake was restricted, usually to 1200 cc. per day, the twenty-four-hour volume of urine measured, and the body weight determined every day or every second day. The period of rest was terminated when it appeared that maximal improvement had been secured, or when the condition of the patient had grown so much worse as no longer to justify the withholding of active medication. In the cases under consideration it varied from four to twenty-two days, with several exceptions which will be discussed. At the conclusion of this preliminary period, digitalis was given in large amounts within a short time. A standardized powdered leaf was the only preparation employed; dosage was calculated on the basis of 0.015 gram per pound of body weight, after deduction for the edema, and this amount was given, in most instances, in from eight to forty-eight hours. A few patients received less than the calculated requirement because symptoms of overdosage appeared early; others were given more than necessary through failure to estimate the edema correctly. Characteristic digitalis effects upon the electrocardiogram—prolongation of the A-V conduction time, inver-

sion of the T wave in Lead 2, or both—were observed in all except two cases; those two patients had bundle branch lesions which obscured the usual digitalis changes. Two or three days were allowed to elapse after the administration of the full dose of digitalis; it was then started in maintenance doses, usually 0.2 gram a day for five consecutive days of each week.

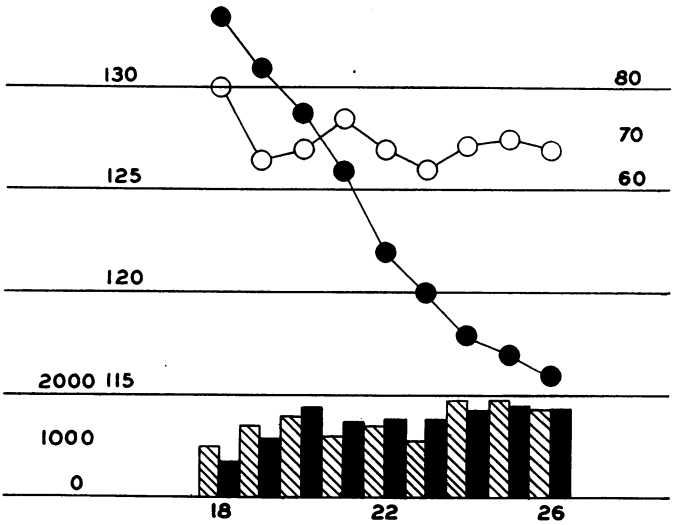

FIG. 1. MALE, AGED 69 YEARS; ARTERIOSCLEROTIC HEART DISEASE WITH CONGESTIVE HEART FAILURE, RHYTHM REGULAR, BLOOD PRESSURE 132/68

No medication whatever; the only treatment consisted of rest in bed with limitation of total fluid intake to 1800 cc. per day. There was slight sustained diuresis with a loss of 17 pounds in 8 days, and disappearance of the signs and symptoms of heart failure. (In this and subsequent figures, fluid intake is indicated by cross-hatched columns, urinary volume by solid columns, heart rate by circles, and weight in pounds by solid dots. Figures in the first column to the left refer to fluid intake and output, those in the second column to the weight; figures for the heart rate are on the right of the chart, and the dates are shown at the bottom.)

If satisfactory diuresis and complete disappearance of edema occurred as a result of digitalis therapy, no other drug was used. If, on the contrary, there was little or no benefit from digitalis, it was followed, after an interval of about a week, by one of more diuretics. The diuretic drugs employed were theophyllin (theocin), theobromine,

theobromine sodio-salicylate, and novasurol; the doses are indicated in the accompanying table.

Attention should be directed to the fact that those individuals who derived the greatest benefit from rest alone are not included in the following analysis. Many patients were selected for study, only to be rejected later because a period of rest without medication caused the complete disappearance of the signs and symptoms of heart failure. The chart of one such patient is shown in figure 1.

So far as possible, all patients with evidence of significant renal damage have been excluded from the group. It is recognized that such evidence is often difficult of interpretation, and chief reliance has necessarily been placed upon the phenolsulphonephthalein renal function test, as customarily used, and upon the level of the blood non-protein nitrogen. These values were determined several times in the majority of patients: at the time of admission to the hospital, and after the clinical condition had changed for better or for worse. Reference to table 1 will indicate that practically all members of the group had normal kidney function as judged by these tests, although a number of the elderly patients continued to show small amounts of albumin and occasional casts in the urine.

While patients were selected for study solely on the basis of rhythm and the presence of advanced congestive heart failure with considerable edema, they have been analyzed in groups based upon the etiologic type of heart disease. Three such groups are included: rheumatic, syphilitic, and arteriosclerotic heart disease. A word of explanation will suffice for the first two; the third group requires brief discussion. Rheumatic heart disease was regarded as present when patients presented unequivocal signs of mitral stenosis, or mitral stenosis and aortic insufficiency, or stenosis and insufficiency of both valves. Adhesive mediastino-pericarditis was also present in some such patients, but was not encountered in the absence of valvular lesions in any subject here included. There was a history of acute rheumatic fever or acute chorea in every member of this group. The diagnosis of syphilitic heart disease was based upon signs of aortic insufficiency, with or without aneurysm, in individuals whose history included syphilitic infection, whose blood Wassermann reaction was strongly positive, and who presented no signs of valvular damage except at the

TAB

Case number	Age	Sex	Duration of study	Blood pressure	Heart rate	Weight	Rest					Digitalis					
							Days	Slowing	Symptoms improved	Loss of weight	Edema-free	Dose	Time	Slowing	Symptoms improved	Loss of weight	Edema-free
Rheumatic																	
			days	*mm.*		*pounds*						*grams*					
1	30	F.	30	110/35	90–110	90*	6	0	0	0	0	1.5	5 days	0	0	0	0
2	29	M.	28	120/60	80–110	120*	3	0	0	0	0	1.6	3 days	0	0	0	0
3	43	F.	39	120/68	80–95	100*	10	0	0	+6	0	1.6	18 hours	0	0	6	0
												1.6	36 hours	0	0	0	0
4	46	F.	63	150/50	80–90	70–75*	8	0	0	+9	0	1.2	1 day	0	0	3 (1 day)	0
5	25	M.	106	120/82	80–110	120*	22	0	0	+10	0	1.8	1 day	0	0	3 (1 day)	0
Syphilitic																	
6	47	M.	28	190–210 / 30–40	Avg. 80	130*	14	0	0	0	0	1.7	30 hours	0	0	0	0
7	45	M.	69	115–160 / 20–60	70–80	148	9	?	Slight	4	0	0.8	1 day	0	0	3 (1 day)	0
8	59	M.	23	170–190 / 80–100	Avg. 85	120	14	0	?	3	0	1.8	2 days	15	++	6 (2 days)	+
9	32	M.	53	130–140 / 70–80	70–80	95	4	20	Slight	0	0	1.4	30 hours	?	+	12 (3 days)	+
10	41	M.	36	126–140 / 44	Avg. 85	120	17	20	Slight	0	0	2.0	1 day	0	++	9 (2 days) 16 (5 days) 22 (9 days)	+
Arteriosclerotic																	
11	69	M.	28	160–178 / 110–130	80–100	142	7	0	0	0	0	1.6	1 day	0	+	25 (5 days)	+
12	62	M.	23	112/60	80–104	112	4	0	0	+4	0	2.8	2 days	10	++	45 (4 days) 58 (10 days)	+

* Estimated.

LE 1

Diuretics				X-ray Diameter heart / Diameter thorax	Electrocardiogram	Non-protein nitrogen	Phthalein excretion
Drug	Dose	Loss of weight	Edema-free				
heart disease							
		pounds		*cm.*		*mgm. per 100 cc.*	*per cent*
Theobromine sodio-salicylate	1.3 gram t.i.d. 6 days	0	0	17.5/23	Normal		41
Theobromine sodio-salicylate	0.6 gram t.i.d. 2 days	0	0	"Very large"	Normal and Vent. PB's		30 (1 hour)
Theobromine sodio-salicylate	0.6 gram t.i.d. 4 days	0	0				33 (1 hour)
Theocin	0.6 gram t.i.d. 2 days	0	0				
Theocin	0.5 gram t.i.d. 2 days	6 (2 days)	0	14/21	Normal	43	70
Theocin (3)	0.3 gram t.i.d. 2 days	6–3–0 (2 days)	0	17/22	Normal	34	45–54
Theocin	0.6 gram t.i.d. 2 days	0	0	"Marked enlargement	Normal	27	61
Theobromine (3)	0.6 gram t.i.d. 2 days	0–1–1	0				
Novasurol (2)	1 cc.—1 cc.	0–0	0				
heart disease							
Theobromine	0.3 gram t.i.d. 2 days	0	0	19.5/24	Normal and Vent. PB's	35	17–55
Theocin	0.3 gram t.i.d. 2 days	0	0				
Novasurol (3)	1 cc.—1 cc.—2 cc.	0–0–0	0				
Novasurol (2)	2 cc.—2 cc.	6–8 (2 days)	0	18.5/30	Normal	39	60
Theocin (2)	0.3 gram t.i.d. 2 days	8–3 (2 days)	+				
Novasurol (before digitalis)	1 cc.	4 (1 day)	0	"Enlarged"	Normal	75–40	24 (adm.)
				17.5/27	Normal	41–29	40–83
				17.5/27	Incomp. Bundle Branch Block	33	45 (adm.)
heart disease							
					Intravent. Block	39	69
				19/28	Very small complexes	33	15–56

TABLE 1

Case number	Age	Sex	Duration of study	Blood pressure	Heart rate	Weight	Rest					Digitalis					
							Days	Slowing	Symptoms improved	Loss of weight	Edema-free	Dose	Time	Slowing	Symptoms improved	Loss of weight	Edema-free
																	Arteriosclerotic heart
			days	*mm.*		*pounds*						*grams*					
13	70	M.	33	130/76	Avg. 70	112	7	0	0	3	0	1.6	2 days	0	+	10 (4 days)	+
14	50	M.	32	120/90	70–80	135	1	0	0	0	0	2.2	3 days	0	+	43 (5 days)	+
15	63	M.	53	132/72	80–95	155	16	0	+	14	0	2.0	30 hours	0	?	3 (2 days)	0
16	56	M.	30	160–210 / 100	Avg. 80	120	8	0	0	+5	0	2.0	1 day	0	Slight	4 (2 days)	0
17	62	M.	30	120/75	80–110	150	7	0	Slight	+3	0	2.2	1 day	0	+	3 (2 days)	0
18	53	F.	75	180–250 / 50–60	80–100	162	10	0	?	+7	0	2.4	2 days	0	0	0	0
19	58	F.	50	128/80	90–106	131	14	0	+	10	0	1.2	2 days	?	+	4 (3 days) 8 (7 days) 13 (10 days)	
20	53	F.	30	155/100	85–100	133	1	0	0	0	0	1.1	1 day	0	0	0	0

In this table, the total length of the period of study is given in the third column, and the number of days of rest without medication in the seventh column. The heart rate given is that at the end of the rest period. The body weight is without edema; if patients failed to become edema-free, the weight was estimated. The figures in the column headed "X-ray" indicate the total transverse diameter of the heart shadow and the transverse diameter of the thorax in the usual seven-foot film. The blood non-protein nitrogen is given in terms of milligrams per 100 cc., and the phenolsulphonephthalein in terms of the percentage excreted in 2 hours 10 minutes after the intramuscular injection of 1 cc. Where two figures are given in these columns, they represent the determinations at the time of admission and after clinical improvement had occurred. The + sign indicates "yes" except in the weight columns, where it means that the patient gained weight instead of losing. The period during which loss of weight occurred is given in days immediately after the figure indicating the loss. Doses are all in the metric system.

aortic orifice. Of the five such patients studied, two had aneurysm of the aortic arch, one had a diffuse dilatation of the ascending aorta, and the remaining two presented clear signs of aortitis. All five had aortic insufficiency.

—*Continued*

Diuretics							
Drug	Dose	Loss of weight	Edema-free	X-ray Diameter heart / Diameter thorax	Electrocardiogram	Non-protein nitrogen	Phthalein excretion
disease—Continued							
		pounds		*cm.*		*mgm. per 100 cc.*	*per cent*
				14.5/27.5	Normal and Vent. PB's	35	70–53
				18/30	Normal	30	75
Theobromine sodio-salicylate	2.6 gram 3 days	8 (5 days)	0	16.5/28	Normal	46 (adm.)	68
Novasurol	2 cc.	4 (2 days)	0				
Theocin	0.3 gram t.i.d. 2 days	3 (2 days)	+				
Novasurol	1 cc.	7 (1 day)	0	"Very	Normal and	42	50
Theocin	0.3 gram t.i.d. 2 days	15 (2 days)	+	large"	Vent. PB's		
Novasurol	1 cc.	3 (1 day)	0	19.5/29	Normal	47	47
Theocin	0.3 gram t.i.d. 2 days	9 (2 days)	+				
Theobromine (2)	0.3 gram t.i.d. 2 days	0–0	0	15.5/21	Normal	30–27–21	57–85
Novasurol (3)	1 cc.—2 cc.—2 cc.	0–0–0	0				
Theocin (3)	0.3 gram t.i.d. 2 days	23–8–8 (2 days)	+				
Theocin	0.3 gram t.i.d. 2 days	14 (2 days)	+		Intravent. Block	39	30 (adm.)
Novasurol (2)	1 cc.—2 cc.	0–0	0	18/25.5	Left Bundle,	41	66
Theocin (2)	0.3 gram t.i.d. 2 days	22–8 (2 days)	+?		Branch Block		

"T.i.d." indicates that the dose mentioned was given three times a day after meals. When diuretics were given more than once, the number of occasions is indicated in parentheses after the name of the drug. Example: Case 18, a woman of 53 years with hypertension, was in the hospital for 75 days. A period of ten days rest caused no slowing of the heart rate, questionable symptomatic improvement, and a gain of 7 pounds in weight. The administration of 2.4 grams of digitalis leaf in 2 days caused no change in heart rate, symptoms, or edema. She received theobromine on two occasions and novasurol on three, without diuresis or loss of weight. Theocin was administered three times, with pronounced diuresis and a loss of 23, 8, and 8 pounds, respectively, the weight loss in each instance occurring in two days. The non-protein nitrogen was normal at three determinations, and the 'phthalein excretion rose from 57 to 85 per cent after the disappearance of edema.

The term arteriosclerotic heart disease is used reluctantly, with a clear realization that it is not entirely satisfactory, but at the same time with the feeling that it is the best yet proposed of those titles which attempt to indicate etiology rather than structural changes or

functional condition. The term assumes that myocardial failure is dependent upon deficient blood flow through sclerosed coronary arteries: an assumption which is often, but not always, supported by

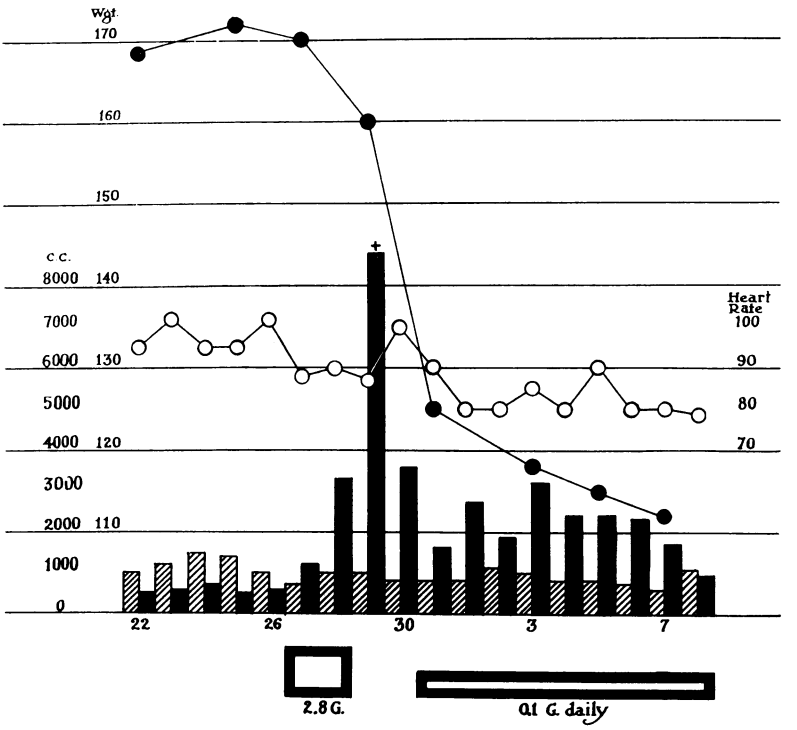

FIG. 2. CASE 12. MALE, AGED 62 YEARS; ARTERIOSCLEROTIC HEART DISEASE, CONGESTIVE HEART FAILURE, REGULAR RHYTHM AND NORMAL BLOOD PRESSURE

Eight days of bed rest at home had caused no improvement, and four days of rest in the hospital resulted in an increase of 4 pounds in weight. The administration of digitalis caused intense diuresis, the urinary volume on one day rising above 9 liters, and a loss of 45 pounds in four days, with a further loss of 13 pounds in the following week. The average heart rate was slightly lowered. Digitalis is indicated by hollow rectangles at the bottom of the chart.

post-mortem examination. As used in this paper, it does not exclude—in fact, it often includes—"hypertensive heart disease." Arteriosclerosis and hypertension as etiologic factors have not been con-

sidered separately because it is so frequently impossible to determine during life which played the dominant rôle in the production of heart failure; they are often, if not always, coexistent. The term "arteriosclerotic" may therefore be read as "arteriosclerotic-hypertensive" by any who feel that the more cumbersome title is the more accurate. The diagnosis of arteriosclerotic heart disease was made in patients who showed evidences of congestive heart failure with cardiac enlarge-

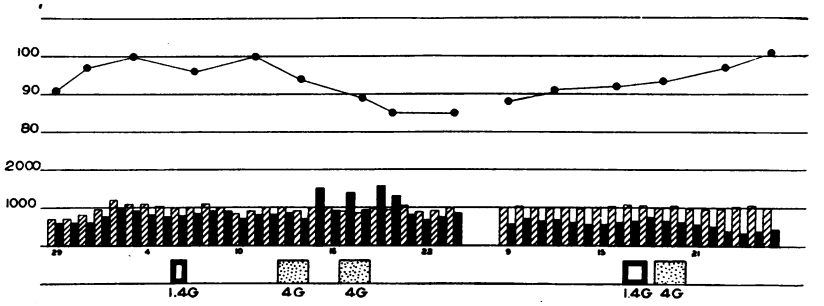

FIG. 3. CASE 4. WOMAN OF 46 YEARS WITH RHEUMATIC HEART DISEASE, CONGESTIVE HEART FAILURE, REGULAR RHYTHM, EXTENSIVE EDEMA. ESTIMATED WEIGHT, 70 TO 75 POUNDS

The upper figures at the left refer to the weight, the lower ones to fluid intake and output. Hollow rectangles below indicate digitalis, stippled rectangles, theocin. Maintenance doses of digitalis, 0.1 or 0.2 gram daily, were given constantly after the first large dose except for one week preceding the second large dose. The gap in the chart indicates an interval of 15 days during which the weight was almost stationary. Notice that digitalis was practically without effect upon the urinary volume or weight. Theocin in twice the usual dosage caused moderate diuresis, with loss of 6 and 3 pounds. Later, however, there was no response to digitalis or theocin. At no time was this patient edema-free. The heart rate was constantly between 80 and 90 per minute except for several days when there was fever.

ment, arteriosclerosis of the peripheral and retinal vessels, and no signs of valve lesions, adherent pericardium, or aortitis. No member of this group was below the age of fifty years, and none had a positive Wassermann reaction.[1]

[1] It is perhaps unnecessary to point out that the diagnosis "arteriosclerotic heart disease" corresponds closely, if not absolutely, with the terms "chronic myocarditis" and "myocardial insufficiency" which are still widely used. Of these two terms, the former is an absolute misnomer and is recognized as such even by those

The number of patients whose response to treatment has been analyzed is twenty, of which five are in the rheumatic group, five in the syphilitic, and ten in the arteriosclerotic. More than forty individuals were originally selected for study, but many had to be excluded because of incomplete data, although satisfactory conclusions could be drawn as to the nature of their response to rest and drug therapy. A few, for example, left the hospital after a stay of less than three weeks (a period which has been arbitrarily taken as the minimum for this study) although it was clear that digitalis had caused greater improvement than had rest alone. Others grew steadily worse despite rest and digitalis, but could not safely be weighed; still others could not have the renal function satisfactorily determined because of urinary incontinence or lack of coöperation. The point which deserves emphasis is that the conclusions drawn from the analysis of twenty illustrative cases are confirmed and strengthened by the study of a much larger number in which the clinical course was clear but the data were incomplete.[2]

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who employ it most consistently; there seems scant justification for its continued use. The latter is but a synonym of "heart failure," and is not in accord with the current belief that etiology is perhaps the most important part of a diagnosis of heart disease. The term used in this paper seems more satisfactory than either of the others in so far as it indicates the only etiology known to exist in many patients with the condition; admittedly, it does not apply accurately to all, and in view of the growing feeling that hypertension is the important cause of heart failure in such individuals, the word "hypertensive" may eventually have to be substituted for "arteriosclerotic."

[2] It would be incorrect, however, to permit the assumption that the total number of rheumatic and syphilitic patients was as great as the total of the arteriosclerotic group. In this clinic, the vast majority of those who have advanced congestive failure with normal rhythm fall into the last-named group; most of the rheumatics with such failure have auricular fibrillation, and congestive heart failure due to syphilis is encountered comparatively infrequently in this locality. Furthermore, relatively few of the small group of rheumatic heart disease with regular rhythm are suitable for study along the lines indicated, as most of them have received digitalis for a long period before their admission to the hospital. The same statement does not apply to the other two groups.

RESULTS

Rest

There is a noticeable difference in the effect of rest upon the signs and symptoms of heart failure in the members of the different groups. The five subjects with rheumatic heart disease showed no evidence of clinical improvement or slowing of the heart rate, and three of them gained weight steadily, the other two remaining stationary. Of the five with syphilitic aortic insufficiency, three showed slight but definite improvement in respiration, and a fourth was probably a little improved; two of them lost several pounds of edema, and in two there was observed a significant reduction in the heart rate. Of the eight members of the arteriosclerotic group whose period of rest was such as to allow conclusions, slowing of the heart rate occurred in none, symptomatic improvement in three, and loss of weight in three. It is to be observed, however, that four of these patients gained weight while at rest, and the increase in weight was accompanied by other evidences of progressing heart failure. Lest these results be regarded with skepticism, as indicating less improvement from rest than has been witnessed by others, it should be reëmphasized that those who derived the greatest improvement were those who lost all of their edema, and were therefore not studied.

Digitalis

With regard to slowing of the heart rate below the level which it reached with rest alone, it may be stated that digitalis apparently caused such slowing in none of those with rheumatic heart disease, in one with syphilitic heart disease, and in one with arteriosclerotic heart disease. This last patient, however, had been at rest for only four days, and the reduction in the average heart rate was only ten beats per minute; the result is by no means conclusive. Significant slowing occurred after the administration of digitalis in two other patients: one with rheumatic, and one with arteriosclerotic heart disease, but in both of them it was due to the production of partial A-V heart block with dropped beats. It is clearly apparent that slowing of the regular heart by therapeutic doses of digitalis occurred almost never in the present group: a finding which is in harmony with the conclusions of practically every other observer.

There was no symptomatic improvement in any patient with rheumatic heart disease after the administration of digitalis; three of them lost a small amount of weight, the loss being inconsiderable, and none became edema-free. Conspicuous improvement in symptoms was noted in two of the syphilitic patients, and less marked improvement in a third; four of the five had diuresis after digitalis, with complete disappearance of edema in three. The results in the arteriosclerotic group were quite different: seven of the ten had definite improvement in symptoms, and an eighth was questionably improved. In a few, the change within a period of one or two days after digitalis was little less than dramatic, and fully equal to that frequently witnessed in patients with auricular fibrillation and excessive ventricular rates. Four of them lost from 10 to 45 pounds in weight within five days or less, and were made edema-free, while four others had moderate diuresis for several days but lost only a portion of their edema. In eight of the ten members of this group, therefore, there was symptomatic improvement and loss of weight which could be ascribed to the action of digitalis.

Diuretics

All of the individuals with rheumatic heart disease received one or more of the xanthine diuretics, and one received, in addition, two doses of novasurol. Theocin caused slight diuresis in two patients, with a loss of 6 pounds in each; the other drugs employed proved useless, and no member of the group was made edema-free by any diuretic. Of the two patients with syphilitic heart disease who remained edematous after digitalis, one responded satisfactorily to novasurol and theocin, and the other grew steadily more edematous despite various diuretics. The six subjects in the arteriosclerotic group who remained edematous after digitalization were all rendered edema-free by diuretics. It happened that theocin was the drug which usually caused the final disappearance of edema, but in several instances it seemed probable that novasurol would have been just as effective. In two subjects, however (nos. 18 and 20), theocin provoked diuresis after novasurol had failed.

A word should be added concerning the several patients whose period of rest was inadequate, or whose dose of digitalis appears too

small. (See table 1.) The subject listed as no. 2 had been in the hospital previously; it was known that rest alone caused no improvement. He had been in bed at his home for thirty-three days, receiving only sedatives, and his condition at the time of entrance was such that it was deemed necessary to administer digitalis very soon in order that diuretics might be given. Inasmuch as all treatment proved ineffective, the inadequacy of the rest period is of no significance. Patient no. 20 had received an unknown amount of digitalis before entrance, and an initial period of rest would therefore have been inconclusive. She was completely digitalized and kept at rest for twenty days, with no improvement whatever; consequently the absence of a rest period is without importance. The only case in which omission of the period of rest may be criticized is no. 14; a man who received digitalis through error. He is included in the group because the extraordinary diuresis which occurred is greater than can be explained on the basis of rest alone; his urinary volume exceeded six liters on several consecutive days, and there was a loss of 43 pounds in five days, with complete disappearance of edema. No attempt is made to indicate that his improvement was due solely to digitalis; there can be little doubt that the drug was responsible for part of it. The small dose of digitalis in case 7 was due to the fact that coupled rhythm invariably appeared after small amounts of the drug. In cases 11 and 19, digitalis was discontinued because of headache and vomiting before the total calculated amount had been given.

COMMENT

Conclusions cannot safely be drawn from the study of this small number of individuals, but certain tendencies seem to be sufficiently apparent to justify brief comment. The feature which has seemed to us most significant is the almost absolute failure of the rheumatic heart to respond to treatment of any sort after the stage of persistent edema has been reached. While that is particularly true of the heart which has maintained its normal rhythm, it is pertinent to indicate that this peculiarity of the rheumatic group may be observed even in the presence of auricular fibrillation. Figure 4, which was published elsewhere to illustrate the effect of digitalis and diuretics in the arteriosclerotic groups, indicates that only 5 of 16 inidividuals with rheumatic heart

disease and auricular fibrillation responded satisfactorily to digitalis, while 18 of 30 similar patients in the arteriosclerotic group were freed of edema. It is generally agreed that the response of the syphilitic heart to treatment is poor: that death usually occurs within two years of the appearance of symptoms. It is of some interest, therefore, that in our experience better results may be expected in syphilitic than in rheumatic patients, if both are selected on the basis of advanced con-

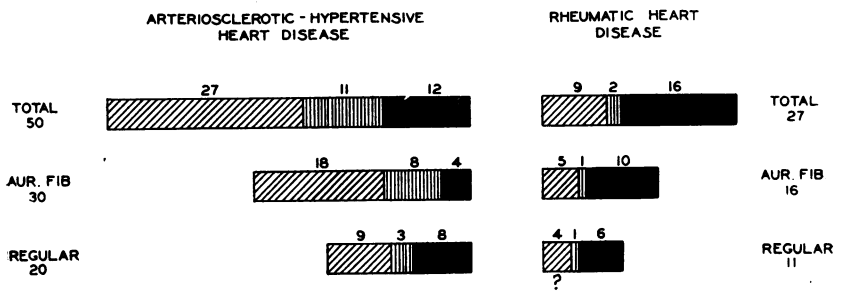

FIG. 4. ILLUSTRATING THE EFFECT OF DIGITALIS AND XANTHINE DIURETICS UPON EDEMA IN PATIENTS WITH CONGESTIVE HEART FAILURE

The total number is shown in the upper column; the lower columns indicate the number with auricular fibrillation and regular rhythm. The portions of the columns in diagonal lines represent the number of patients who were freed of edema by digitalis alone, and the portions in vertical lines the number made edema-free by diuretics after digitalis had failed. The black sections indicate the number who retained part or all of their edema after digitalis and diuretics had been given repeatedly. Notice the great relative size of the black portions in the rheumatic group, even in those with auricular fibrillation. It should be noted that this chart is based solely upon the presence or absence of edema; it takes no account of symptomatic improvement. Many patients of the present series are not included in the above figures. The question mark beneath the lowest column on the right indicates that the improvement in those four individuals was probably not due solely to digitalis.

gestive heart failure with regular rhythm and considerable persistent edema. It should be added, however, that the improvement in our syphilitic patients, as in those of Scott (6), was only temporary. The far better response of the arteriosclerotic patients to treatment is so apparent as to require no emphasis. Eight of our ten patients in this group were benefited by digitalis; all were made edema-free by digitalis or diuretics.

Four of the rheumatic group died within two months, and the fifth in eleven months, after the beginning of active treatment. Four of the syphilitic patients died in one, five, six and seven months, respectively; the other is alive nine months after discharge from the hospital. Of the ten subjects in the arteriosclerotic group, five are known to be alive after periods of from four to twenty-six months, two are known to have died (one of them from pneumonia), and three cannot be traced.

It will probably be urged that the rheumatic and arteriosclerotic groups are not comparable, inasmuch as the patients in the former were near death while those in the latter were not. One purpose of this paper is to direct attention to that very fact: that the signs and symptoms usually regarded as indicating advanced heart failure represent a later stage of failure in the rheumatic than in the arteriosclerotic patient. It is quite conceivable that differences of opinion concerning the beneficial action of digitalis in heart failure may have arisen through failure to select similar patients for treatment; the basis on which selection should be made seems to us not merely the cardiac rhythm or the presence of edema, but the etiology, the rhythm and the presence of edema. If one investigator treats chiefly patients with rheumatic heart disease, and another deals almost exclusively with arteriosclerotic subjects, it is not strange that their conclusions are divergent.

Let it be clearly understood that the patients under discussion are not those with dyspnea on exertion and occasional transient edema of the lower extremities. They are individuals whose heart failure has progressed to such a point as to force the abandonment of physical activity and their confinement to bed. When this degree of failure has occurred as a result of rheumatic disease, it is seldom indeed that restoration to active life is achieved; when it has resulted from the arteriosclerotic type of heart disease, restoration to useful, though restricted, activity is often observed after rest and digitalis therapy. The syphilitic group apparently stands between the other two, although many such patients pursue the rapid downward course which characterizes the advanced failure of rheumatic heart disease.

The results in the present series of patients can be compared satisfactorily only with those obtained by Luten (1). Of his ten patients with "chronic myocarditis" (half of whom had chronic nephritis also),

nine were definitely improved by digitalis administered after a preliminary rest period, while eight of our ten with arteriosclerotic heart disease were similarly benefited. Of four cases listed as syphilitic in table 1 of his article (nos. 5, 8, 17, 18), two were improved by digitalis and two were not: results slightly less favorable than those in the present group. His case 2 is listed simply as "aortic insufficiency" but the Wassermann reaction was strongly positive and it seems probable that the valvular lesion was syphilitic rather than rheumatic, despite the age of 22 years. If that patient be grouped with the other four, it makes the results in his group and in our own almost identical. Only one of Luten's twenty patients can be classed as rheumatic heart disease (no. 7); that one was apparently improved by digitalis, but the incomplete data given indicate only slight improvement.

The observations detailed above require confirmation and extension before they can be used as a basis for definite conclusions. That is particularly true of the rheumatic and syphilitic groups, for the results in the arteriosclerotic group merely confirm the findings of many previous writers, and can scarcely be regarded as accidental. The study of this small number of patients appears to indicate that under the circumstances mentioned, digitalis and diuretic drugs yield excellent results only when administered to those with the arteriosclerotic type of heart disease. Occasionally, patients with syphilitic heart disease respond satisfactorily for a short time, but those with rheumatic heart disease do so very infrequently.

A consideration of the reason or reasons for this peculiarity of rheumatic heart disease is not here in place. Suffice it to say that in only one patient of the present group was there any evidence of infection; that one had occasional slight fever and transient leucocytosis. That a reactivation of the process in the heart may be responsible for the steady downward course of many of these individuals is suggested by a number of facts. The belief that these patients had reached a later stage of heart failure than the others has already been indicated.

CONCLUSIONS

The administration of digitalis in suitable large doses under properly controlled conditions to patients with advanced congestive heart failure, regular rhythm, and considerable edema, appears to cause im-

provement consistently in only one group: the group here designated "arteriosclerotic heart disease," but frequently referred to as "chronic myocarditis" or "myocardial insufficiency." The drug has been found occasionally beneficial in patients with syphilitic heart disease, but almost devoid of effect in rheumatic heart disease.

The same differences have been noted with regard to the effectiveness of diuretic drugs administered after complete digitalization. Individuals with rheumatic heart disease seldom show satisfactory diuresis; those with arteriosclerotic heart disease, as a rule, respond in a highly favorable manner.

The foregoing statements are supported by the results in twenty illustrative cases analyzed in the accompanying table, but are actually based upon the study of more than twice that number.

It is suggested that differences of opinion concerning the effect of digitalis in heart failure with normal rhythm may depend in part upon differences in the patients selected for treatment. It is believed that a division of patients upon the basis of etiology of the heart disease is essential for the proper correlation of the results of different observers.

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